



08-05-03

AF/1625

PATENT APPLICATION

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): Paul A. Renhowe *et al.*

Serial No.: 09/943,382

Filed: August 30, 2001

Title: **HETEROCYCLIC DERIVATIVES OF QUINOLINONE
BENZIMIDAZOLES**

Docket No.: 072121:0139

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
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Date of Deposit: August 4, 2003

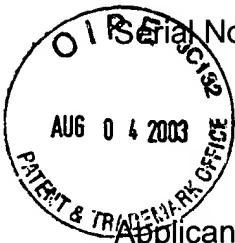
I hereby certify that these attached documents

- * Request for Reconsideration Under 37 C.F.R. § 1.116 (12 pages)
- * Duplicate of page 1 and signature page
- * Return postcard

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Enclosed for filing please find the above-referenced documents. Please indicate receipt of these documents by returning the attached postcard with the official Patent and Trademark Office receipt stamped thereon.

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16325.002

PATENT APPLICATION

#26
JAN
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Paul A. Renhowe et al.

Title: HETEROCYCLIC DERIVATIVES OF QUINOLINONE BENZIMIDAZOLES

Appl. No.: 09/943,382

Filing Date: August 30, 2001

Examiner: Rita J. Desai

Art Unit: 1625

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REQUEST FOR RECONSIDERATION UNDER 37 C.F.R. § 1.116

MAIL STOP AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Examiner:

This is in reply to a final Office Action mailed on June 2, 2003. The shortened three-month statutory period for response to the Office Action expires on September 2, 2003, and the period for response within the Advisory period expires on August 2, 2003. Because August 2, 2003, falls on a Saturday and Monday, August 4, 2003, is the next business day, this response is timely filed within the Advisory period.

Applicants do not believe that any fee is due for this filing. However, should any fee(s) be due, the Commissioner is hereby authorized, under 37 CFR §§ 1.16-1.17, to charge any fee that may be due to Deposit Account No. 50-2350. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 50-2350. Duplicates of page 1 and the signature page are enclosed for such purpose.

REMARKS

Applicants thank Examiner Desai for including the Examiner-initialled copy of the various information disclosure statements previously submitted in this application along with the final Office Action. Applicants also take this opportunity to thank Examiner Desai and her Supervisor, Alan Rotman, for granting the Interview of July 31, 2003. Also in attendance were Applicants' attorneys, Richard C. Peet and Bernard P. Friedrichsen. During the Interview, the Restriction Requirement, Response to Restriction Requirement, Ex Parte Quayle Action and the new restriction imposed therein, the Response to the Ex Parte Quayle Action, and the final Office Action were discussed. Applicants explained how the amendments filed in response to the Ex Parte Quayle Action were in accordance with the new restriction requirement imposed by the Examiner in the Ex Parte Quayle Action except as explained in greater detail below. Applicants also explained why the additional restriction requirement described below was particularly onerous to Applicants and how the independent claim could be searched without imposing any additional serious burden on the Examiner. Applicants took the opportunity to show that no prior art relevant to the compounds of claim 1, or indeed any of the other claims had been set forth. During the Interview Examiner Desai requested that, when filing a response to the final Office Action, Applicants include: (1) examples of compounds with heterocycles; and (2) examples of compounds in which R⁵ and R⁶ of formula I of claim 1 are not heterocyclic groups. Examiner Desai agreed to reconsider the following additional restriction requirements imposed in the Ex Parte Quayle Action:

1. One of R⁵ and R⁶ is a heterocyclic ring and the other of R⁵ and R⁶ is H; and
2. All other R groups are non-heterocyclic groups and non-heterocyclic ring containing groups.

Claims 1-8, 18, 19, and 22-29 are currently pending in the application.

None of the claims is amended by this Request for Reconsideration under 37 C.F.R. § 1.116. Each of pending claims 1-8, 18, 19, and 22-29 is objected to in the final office action dated June 2, 2003. None of the claims has been rejected in view of any prior art reference.

In view of the following remarks, Applicants respectfully request reconsideration and withdrawal of the objections and additional restriction requirement which is particularly onerous to Applicants. Applicants respectfully submit that the application is in condition for allowance.

BRIEF HISTORY OF RESTRICTION REQUIREMENTS AND RESPONSES

A brief history of the prosecution of this application may be helpful. First, a Restriction Requirement was purportedly mailed to Applicants on April 17, 2002. Applicants did not receive the Restriction Requirement, but became aware of it on October 16, 2002 when using PAIR to check the status of the application. Upon request, Examiner Desai sent a copy of the April 17, 2002 Restriction Requirement to Applicant's attorney via facsimile. The Restriction Requirement divided the claims into six different groups, required that Applicants elect one Group for prosecution, and additionally required that Applicants elect a single disclosed species for prosecution. Groups I, II, and III each included claims 1-8 and 18, but divided independent claim 1 by defining what the variables in the chemical structure could be. Groups IV and V both included claims 9-17 and 20, but divided independent claim 9 by defining what the variables in the chemical structure could be. Finally, Group VI included claim 19 and 21 drawn to methods of treating diseases using the compounds of claims 1 and 9 of the other Groups. The specific restriction requirement imposed with respect to Groups I, II, and III is provided below:

I. Claims 1-8 and 18 all in part, drawn to compounds and pharmaceutical compositions of compounds of formula I wherein Y is NR¹⁰R¹¹, OH, OR⁸, Z is NR¹³, R¹ and R² do not together form a ring, all other R are non-hetero ring containing, classified in class 546, 514, subclass 272.8, 268.4, 322. (emphasis added).

II. Claims 1-8 and 18 all in part, drawn to compounds and pharmaceutical compositions of compounds of formula I wherein Y is NR¹⁰R¹¹, OH, OR⁸, Z is NR¹³, R¹ and R², together form a ring, containing S or O as a hetero atom all other R are non-hetero ring, classified in class 546, 514, subclass 114, 115, 300.

III. Claims 1-8 and 18 all in part, drawn to compounds and pharmaceutical compositions of compounds of formula I other than in Groups I and II, classified in various classes and subclasses.

On October 17, 2002, Applicants filed a Response to Restriction Requirement along with a 5-month petition for extension of time shortly after they became aware of the outstanding restriction requirement. In the Response, Applicants elected the claims of Group III with traverse, elected a species as required, and canceled claims 9-17, 20, and 21. Applicants traversed the restriction imposed between Groups I, II, and III and noted that Group I was an improper group because it required that R¹ and R² do not together form a ring when claim 1 specifically sets forth that they do form a ring. Applicants further traversed the restriction between claim 19 of Group IV and the claims of Groups I, II, and III and noted that claim 19 should be rejoined with Group III because it is directed to method of treating that uses the compound of claim 1.

An Ex Parte Quayle Action, responsive to Applicant's October 17, 2002 Response, was purportedly mailed to Applicants on December 18, 2002. Examiner Desai immediately sent a copy of the Action to Applicant's attorney via facsimile on February 13, 2003, when Applicants became aware of the Action while using PAIR. In the Ex Parte Quayle Action, the Examiner (1) required that the title of the application be changed, (2) imposed additional restriction requirements to the only independent claim of elected Group III, (3) rejoined claim 19 with the compound claims, (4) objected to claims 2-4 for failing to further limit the further restricted claim 1, (5) noted that claims 1, 5-8 and 18 and 19 would be allowable if amended to exclude the non-elected subject matter, (6) analyzed the closest prior art found by the Examiner, and (7) closed prosecution on the merits.

Because Applicants were uncertain about the specific extent of the newly-imposed restriction on the compounds of Group I in the Ex Parte Quayle Action, and felt that such restrictions were particularly burdensome and yet might be resolved by Interview, Applicants requested a telephonic Interview with the Examiner. During the telephonic Interview of February 25, 2003, Examiner Desai clarified the expanded restriction requirement which was imposed on the claims of the application. Examiner

Desai explained that the following new restrictions were imposed on the compounds of the single independent claim (claim 1) of Group III:

1. Y is a -NR¹⁰R¹¹ group;
2. Z is a NR¹³ group;
3. R¹ and R² join together to form a substituted or unsubstituted 6-membered ring comprising at least one O, N, or S atom;
4. One of R⁵ and R⁶ is a heterocyclic ring and the other of R⁵ and R⁶ is H; and
5. All other R groups are non-heterocyclic groups and non-heterocyclic ring containing groups.

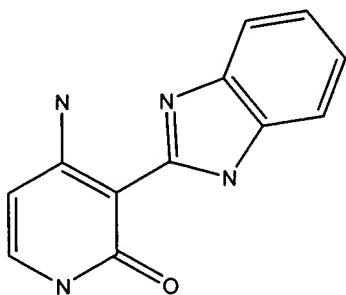
Applicants filed an Amendment and Response to the Ex Parte Quayle Action on March 12, 2003. In the Amendment and Response, Applicants amended claim 1 to conform to the first three additional restriction requirement parameters set forth in paragraphs 1-3 set forth above. Specifically, because Applicants are reasonable and wished to obtain rapid allowance, they amended claim 1 so that Y is an -NR¹⁰R¹¹ group; so that Z is an NR¹³ group; and so that R¹ and R² join to form a 6 membered ring comprising at least one O, N, or S atom. Applicants further explained how the amendment provided a scaffold that could be readily searchable. Applicants amended claims 2-5 in light of the amendment of claim 1 and added new claims 22-29. Therefore, Applicants mostly amended the claims to conform with the newly imposed restriction requirement. Applicants also explained why the restriction requirement parameters set forth in paragraphs 4 and 5 should not be necessary for the Examiner to conduct her search and should not impose any additional burden on the Examiner. Applicants further explained why these additional restriction parameters were extremely burdensome and onerous to Applicants, particularly in light of the other restriction parameters imposed on this application. Applicants also amended the title in accordance with the Ex Parte Quayle Action. However, Applicants respectfully asserted that they are entitled to broader claim coverage and scope than that imposed by the full expanded restriction requirement. Therefore, Applicants respectfully traversed the expanded restriction requirement imposed in the Ex Parte Quayle Action and reserved the right to challenge the restriction requirements imposed on this application.

In the Amendment and Response to the Ex Parte Quayle Action

Applicants respectfully submitted that the Ex Parte Quayle Action was improper. As noted in § 714.14 of the MPEP, an Ex Parte Quayle Action should be issued only when all claims in an application have been allowed and only formal matters remain. Here, the Examiner imposed an additional particularly onerous restriction requirement without providing Applicants with any ability to respond or for that matter even decide what Group they would elect. Applicants have paid the requisite filing fees and submit that they are entitled to examination of the application and the remaining claims after the initial restriction requirement. Applicants noted that because the additional restriction requirements imposed in the Ex Parte Quayle Action were so restrictive and the various Markush groups of the single independent claim were narrowed so severely, none of the other dependent compound claims (claims 2-8) even fell within the scope of the narrowed claim prior to amendment. Applicants further noted that no prior art had been cited which is relevant to the patentability of the elected species or even claim 1 as it was filed. Therefore, Applicants cited § 803.02 of the MPEP noting that the further restriction requirement imposed in this application was improper.

SUMMARY OF THE FINAL OFFICE ACTION

A final Office Action was mailed to Applicants on June 2, 2003, responsive to the Amendment and Response to Ex Parte Quayle Action filed by Applicants on March 12, 2003. The final Office Action objected to each of claims 1-8, 18, 19, and 22-29 and made the restriction requirement final. The Examiner stated that the traversal is not convincing since Applicants' core as given by the following structure is not novel and has numerous iterations:



Specifically, the Examiner referred to a sample search with the following parameters:

=>s11

SAMPLE SEARCH INITIATED 17:14:53 FILE 'REGISTRY'

100.0% PROCESSED	104 ITERATIONS	0 ANSWERS
SEARCH TIME:	00.00.01	

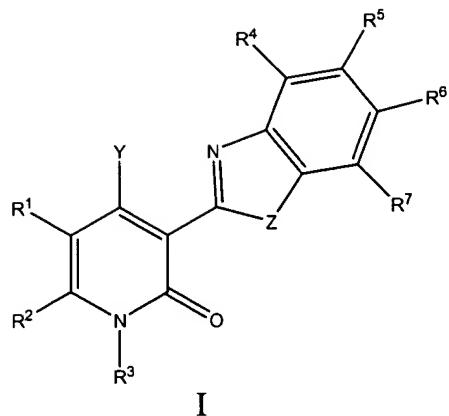
PROJECTED ITERATIONS: 1469 TO 2691

Based on the above sample search, the Examiner concluded, "Thus applicants core is not a contribution to the novelty of the invention." The Examiner further noted that the different variables along with the hetero groups and non hetero groups are classified in numerous classes and subclasses such that the search is burdensome. The Examiner also referred to two references, DE 3634066 and WO 92/18483 to support her contention that the core is not Applicants contribution over the prior art. Finally, the Examiner stated the following:

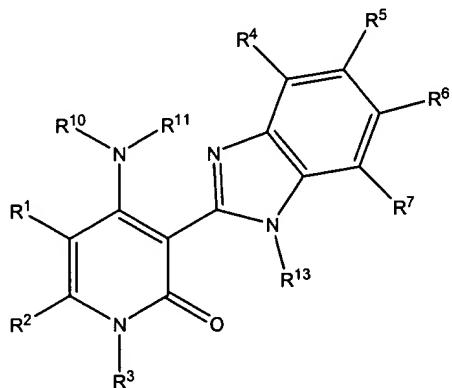
1. The applicants have not cancelled claims that would be essential duplicates for example claims 25 and 27.
2. Also the various variables with the numerous heterocycles are also still in the claims; and
3. Claim 1 is not limited to R⁵ and R⁶ being a heterocyclic ring.

SPECIFIC REMARKS WITH RESPECT TO FINAL OFFICE ACTION

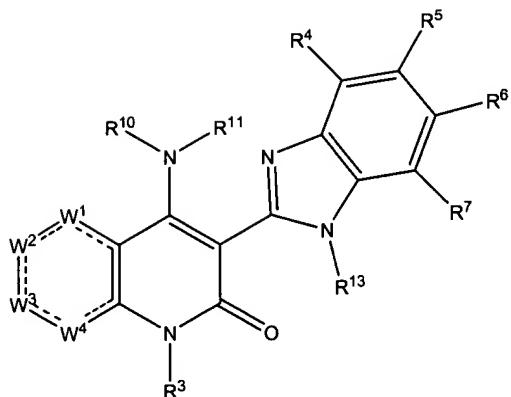
Claim 1 is the only independent claim pending in this application. As described above, Applicants amended claim 1 to conform with the first three of the five paragraphs set forth in the new restriction requirement imposed against the claims in the Ex Parte Quayle Action. Claim 1 is thus drawn to "A compound having the structure I, a tautomer of the compound, a pharmaceutically acceptable salt of the compound, or a pharmaceutically acceptable salt of the tautomer." Structure I has the following formula:



where, as currently amended, Y is an $-NR^{10}R^{11}$ group, Z is an NR^{13} group, and R^1 and R^2 join to form a 6 membered substituted or unsubstituted ring comprising at least one O, N, or S atom. Thus, on pages 7 and 8 of the Amendment and Response to Ex Parte Quayle Action filed on March 12, 2003, Applicants submitted that the amendments to claim 1 provided an adequate scaffold that could be readily searched and which should have been sufficient to allow the Examiner to perform a rapid and simple search for the compound. The scaffold presented by Applicants is presented below:



With respect to this structure, Applicants specifically noted that the structure to be searched should be that where R^1 and R^2 join to form a 6 membered ring that comprises at least one O, N, or S atom as set forth in amended claim 1. Thus, the structure that Applicants previously recommended could be searched can be represented by the following structure:



where at least one of the variables W¹, W², W³, or W⁴ is a O, N, or S atom.

In contrast to the provisions of amended claim 1, the structure of the compound searched by the Examiner in the sample search apparently did not include the provision that R¹ and R² join together to form a 6 membered ring comprising at least one O, N, or S atom. Applicants respectfully submit that this may account for the numerous iterations projected in the sample search. As explained during the Interview of July 31, 2003, and noted again here, Applicants stress that the present application published on August 2, 2002 as 2002/0103230 A1 and that the corresponding PCT application PCT/US01/41942 published on March 7, 2002, as WO 01/18383 A2. Any search directed to the compounds of claim 1 at this date should find hits corresponding to these publications which are not prior art. Therefore, the Examiner should be aware that she should obtain hits, but that such hits may not represent prior art and may represent the present application or the corresponding PCT application.

As noted above, the Examiner conducted a sample structure search based on the structure presented above (page 6 of this response) and concluded that the core structure of claim 1 is not novel because of the number of iterations projected by the search. Applicants respectfully note that this is not an approved standard used to determine patentability and/or restriction in the United States. Rather, the sample search conducted by the Examiner with a broader structure than appropriate (see above) went through 104 iterations and was performed after the present application and corresponding PCT application had been published. Yet after 104 iterations of the projected 1469 to 2691 iterations, 0 answers were found. Applicants question why the full search was not performed given that 0 answers were found even after roughly 7%

(104/1469) of the projected iterations had been performed. Thus, rather than support the Examiner's contention that Applicants' core is not novel, Applicants respectfully submit that the search very well supports the patentability of claim 1 and also shows that the search could be performed even without restricting R¹ and R² to forming a 6 membered ring comprising at least one O, N, or S atom rather than a 5 to 7 membered ring comprising at least one O, N, or S atom as initially set forth in claim 1. Applicants respectfully contend that the Examiner can conduct the search with claim 1 using the structure and provisions noted above being mindful of Applicants' own non prior-art publications. Applicants finally note that a large number of answers in such a search may not necessarily indicate a large number of documents as each compound will be shown as an answer rather than each document.

As noted above, the Examiner further cited DE 3634066 and WO 92/18483 for her conclusion that Applicants' core is not a contribution over the prior art. Applicants respectfully submit that this is simply not correct. First, Applicants note that WO 92/18483 was submitted by Applicants in their Information Disclosure Statement filed on February 26, 2002, and again in their Information Disclosure Statement filed on October 2, 2002. If the Examiner wishes to reject the claims based on either of these references, then the Examiner should reopen prosecution and allow Applicants to have their case examined. At the least, the Examiner should explain why either of these references is relevant to the claims of the present application. Applicants request that the Examiner to articulate her position clearly so that they can formulate a response. Notably, each of the prior art references cited in the Ex Parte Quayle Action (WO 01/28993, US 6,479,512, and WO 01/29025) was discussed by Applicants and shown not to be relevant to any of the claims of the application for the reasons set forth on pages 6 and 7 of the Amendment and Response to the Ex Parte Quayle Action.

Finally, because Applicants respectfully submit that the only independent claim (claim 1) in the application can be readily searched for the reasons presented above, and Applicants have amended the claims to comport with the majority of the Examiner's numerous restriction parameters in order to obtain early allowance, Applicants should not have to further amend the claims to further read that

1. One of R⁵ and R⁶ is a heterocyclic ring and the other of R⁵ and R⁶ is H; and
2. All other R groups are non-heterocyclic groups and non-heterocyclic ring containing groups.

During the Interview of July 31, 2003, Examiner Desai requested that Applicants supply her with examples which include heterocycles and those in which neither R⁵ nor R⁶ is a heterocycle. Examples of compounds in which neither R⁵ nor R⁶ is a heterocycle include Examples 1-3, 5, 6, 9, and 14-18. In Examples 1, 3, 9, and 14-18, both of R⁵ and R⁶ are H. In Example 2, R⁵ is CH₃ and R⁶ is H. In Example 5, R⁵ is a morpholinylethoxy group and R⁶ is an H. In Example 6, R⁵ is a group of formula -C(=O)-N(CH₃)₂ and R⁶ is H. Examples of compounds which include heterocyclic group include the following: Examples 4, 8, and 12 where R⁵ is a dimethylamino-pyrrolidine group; Example 5 where R⁵ is a morpholinylethoxy group (R¹⁴ is a morpholinylethyl group); Examples 7 and 11 where R⁵ is a morpholine; Examples 10 and 13 where R⁵ is an N-methylpiperazine group; Example 15 which includes a pyrazole group; Example 16 which includes a thiophene group; Example 17 which includes an imidazole group; and Example 18 which includes a 1-methyl-1H-pyrazole group.

For all of the above reasons, Applicants respectfully submit that it is not proper (see § 803.02 of the M.P.E.P. as described above) and should not be necessary to further restrict amended independent claim 1, and Applicants respectfully request that the Examiner reconsider and withdraw the objections to the claims and allow the patent to issue. Applicants continue to preserve their right to petition the initial restriction requirement imposed between the claims of Groups I, II, and III, to petition the additional restriction requirement imposed in the Ex Parte Quayle Action and the procedural use of the Ex Parte Quayle Action to force Applicants to agree with the Examiner's restriction requirement, and to petition the further restriction, particularly with respect to additionally requiring that one of R⁵ or R⁶ be a heterocycle while the other is a H and to requiring that none of the other R groups can be a heterocycle. Applicants thank Examiner Desai for her time and consideration.

CONCLUSION

In view of the above remarks, it is respectfully submitted that this application is in condition for allowance. Early notice to that effect is earnestly solicited. The Examiner is invited to telephone the undersigned at the number listed below if the Examiner believes such would be helpful in advancing the application to issue.

Respectfully submitted,

Date August 4, 2003

By 

FOLEY & LARDNER
Customer Number: 23524



23524

PATENT TRADEMARK OFFICE

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